XENOBIOTIC COMPOUND MODULATED EXPRESSION SYSTEMS AND USES THEREFOR

ABSTRACT

A novel nuclear receptor, termed the steroid and xenobiotic receptor (SXR), a broad-specificity sensing receptor that is a novel branch of the nuclear receptor superfamily, has been discovered. SXR forms a heterodimer with RXR that can bind to and induce transcription from response elements present in steroid-inducible cytochrome P450 genes in response to hundreds of natural and synthetic compounds with biological activity, including therapeutic steroids as well as dietary steroids and lipids. Instead of hundreds of receptors, one for each inducing compound, the invention SXR receptors monitor aggregate levels of inducers to trigger production of metabolizing enzymes in a coordinated metabolic pathway. Agonists and antagonists of SXR are administered to subjects to achieve a variety of therapeutic goals dependent upon modulating metabolism of one or more endogenous steroids or xenobiotics to establish homeostasis. An assay is provided for identifying steroid drugs that are likely to cause drug interaction if administered to a subject in therapeutic amounts. Transgenic animals are also provided which express human SXR, thereby serving as useful models for human response to various agents which potentially impact P450-dependent metabolic processes. Also provided are expression systems and expression vectors having SXR receptors and the like operably linked to target genes of interest.